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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,034	05/25/2001	David Botstein	P2930R1C1	4767

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,034	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/20/2005 has been entered.

Claims 27 and 33-37 are pending and under consideration.

The information disclosure statement filed 6/20/2005 has been considered. References 30, 34, 35, 45 and 46 have not been considered as they are already of record in this case. Applicants are reminded to avoid duplicate citations.

Objections and Rejections under 35 U.S.C. §101 and §112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27 and 33-35 remain, and newly introduced claims 36 and 37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for reasons cited in the previous Office Action mailed 2/9/2004 , at pages 2-4.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 33-35 remain, and newly introduced claims 36 and 37 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants traversal filed 6/20/2005 has been fully considered but is not deemed persuasive.

At page 7 of the response, applicants allege that "those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene amplification, gene expression, and protein expression." This argument has been fully considered but is not deemed persuasive because this is simply not the case. The person of ordinary skill in the art, finding the amount of DNA amplification reported for PRO1800 would *not* presume the protein to be overexpressed, for reasons of record, but would be likely to perform the quite simple experimentation required to determine that fact, namely looking for expression of the protein itself. Also at page 7, applicants argue that they do not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty. The Examiner concurs. No such requirement is being made here. Rather, the Examiner has established a *prima facie* case of lack of utility, based upon the standards used in the art. Applicant has failed to overcome the *prima facie* case by presentation of any persuasive facts, or notably, by submission of any evidence. A similar argument is made at page 9, and is similarly not persuasive. It remains that the preponderance of the evidence points to a lack of predictability, and applicants have provided no facts or evidence to the contrary.

At page 8 (and again at page 9), applicants allege that "in a significant number of samples the amplification (of DNA encoding PRO1800 polypeptide) is greater than four fold (Ct value greater than 2.0)." This is contrary to the facts as presented in the specification. At page 117 of the specification, it is disclosed that eight of eighteen colon adenocarcinoma primary tumors had Ct values of greater than one. *None* of those had a Ct of two or greater. With regard to primary lung tumors, one adenocarcinoma was tested (LT12), in triplicate, with an average Ct value of 1.88. One mixed adenocarcinoma/squamous cell carcinoma was tested (LT13) in duplicate, with an average Ct value of 1.8. Six squamous cell carcinomas were tested, only *one*

of which (LT19) showed an average Ct value of more than 2. finally, a single LCC was tested (LT21), with a Ct value of 1.3. Accordingly, applicants assertion that a significant number of samples had a Ct value greater than 2.0 is at odds with the facts.

At page 10, applicants argue that nothing in the Sen reference is contrary to applicants assertion that there is a reasonable correlation between gene amplification and gene overexpression. This argument has been fully considered but is not deemed persuasive because Sen is cited to establish that aneuploidy is a well known characteristic of tumors, and is the most parsimonious explanation for an increased copy number of DNA; it is not suggestive of a causal effect between the existence of the tumor and the overexpression of any genes on the amplified chromosome. More simply put, just because DNA is amplified 2-3 fold in a minority of tumor isolates is *not* predictive that that particular DNA, or the protein encoded by it, is diagnostic of such tumors. It would appear to be no more than random. In fact, applicants data supports this interpretation with respect to the lung cancers tested. With respect to the colon cancers, the evidence is more compelling, but only to the effect that one would expect colon tissue with increased copy number of PRO1800 to be potentially cancerous; it remains that it is not predictable whether the protein itself would occur at increased levels. Further, applicants arguments are focusing on only two of the references cited; in the Office Action mailed 3/22/2005, several additional references were cited to demonstrate that the person of ordinary skill in the art would not consider the data in the specification to support an assertion that the encoded protein would be more likely than not overexpressed at a detectable level.

At pages 10-11 applicants suggest that Pennica's results were artifactual. Such is not persuasive, as it is not substantiated by fact or evidence. It remains that the preponderance of *evidence* in this case is that it is not predictable that PRO1800 protein is overexpressed significantly such as to enable a diagnostic method. Hence the protein itself has not utility. Applicants arguments at pages 12-16 of the response are duplicative of previous arguments, and have been fully addressed on the record.

At page 16, applicants argue that the Alitalo reference provides "sufficient evidence that in all of the amplified genes studied there is a reasonable correlation between gene amplification and mRNA expression." This argument has been fully considered but is not deemed persuasive because it is not correct. Alitalo started with *proteins that were known to be overexpressed*, and

then looked at gene amplification, the exact opposite of the situation with PRO1800. All of the genes found to be amplified were associated with increased protein expression, because increased protein expression was the initial criterion. Proteins that were not overexpressed were not studied. See the Examiners response to this argument at page 4 of the office action mailed 3/22/2005.

With respect to Merlino and Bahnassy, at page 17 of applicants arguments, having first brought these references to the record, applicants now assert that the factual distinctions between those references and the facts regarding PRO1800 are not relevant. On the contrary, the identity of the genes examined by those authors is important, as growth factors are known to be a causative factor in tumor growth, such that *if* it has been asserted that PRO1800 was a growth factor gene, it would lend credence to the assertion that the protein would be expected to be overexpressed in cancer. However, there is no such correlation for Hep27, which is stated to have unspecified homology to PRO1800, nor is PRO1800 asserted to have any biological activity that would reasonably be expected to be correlated with a cancerous state.

With respect to Hanna, at page 20 of the response applicants argue that Hanna states that FISH and IHC results generally correlate well. Hanna does indeed state this. FISH stands for fluorescent in situ hybridization, in which protein is visualized in the affected tissue, and IHC stands for immunohistochemistry, in which the amount of HER-2/neu protein present on the cell membrane is visualized. In other words, Hanna teaches that both methods of *looking at the protein directly* are comparable. This has no bearing whatsoever on applicants assertion that gene amplification leads to protein overexpression.

Applicants arguments of Ornoft are not pertinent. Ornoft correlated DNA with mRNA and protein. The specification merely looks at DNA. hence, a correlation between mRNA level and protein is not pertinent here, as there has been no demonstration of elevated mRNA levels, nor is it predictable, based upon the prior art of record, that such would occur.

With respect to Hyman, applicants seek to have their cake and eat it, too. Applicants argue that because Hyman does not examine protein expression it is not relevant, and then argue that "evidence of a prominent global influence of copy number changes on gene expression levels" should be persuasive. Plucking a single general statement from the reference does not negate the teachings therein. The Examiner cannot manufacture data, but must look to what is

reported in the art to establish the state of the art. Retrospective studies are useful for establishing such. It remains that the Examiner has established, citing Sen, Pennica, Hu, Hanna, Orntoft and Hyman the type of experimentation that is carried out in the art to establish the correlation between overexpression of a protein and cancer diagnosis, and further that a mere two-fold amplification of the DNA (not mRNA and not protein) would not be considered by a person of ordinary skill in the art to be predictive of protein overexpression. It remains that applicants seek to discredit references by piecemeal analysis, while failing to provide any fact or evidence relating to the particularly claimed protein, PRO1800.

The Grimaldi and Polakis declaration, as well as the Lewin textbook have previously been considered, and remain non-persuasive for reasons of record.

Applicants argue that the paper by Zhigang shows that there was a high correlation between mRNA levels and protein for prostate stem cell antigen. This argument has been fully considered but is not deemed persuasive because there is no information on mRNA levels of PRO1800.

No publication by Meric (Molecular Cancer Therapeutics 2002) accompanied applicants submission of 6/20/2005. Accordingly the Meric reference will not be addressed.

The Declaration by Victoria Smith under 37 CFR 1.132 filed 6/29/2005 and dated 1/20/2005 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§101 and 112, first paragraph as set forth in the last Office action because:

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the nature of the fact sought to be established is whether or not PRO1800 protein is over expressed in lung tumors. Paragraph 4 of the declaration clearly states that DNA samples were used in the microarray studies. According to Dr. Smith's characterization, the PRO1800 DNA was present in significantly increased copy number in nine of eighty samples. Based upon that result, Dr. Smith concludes that the gene is

over expressed in those samples. This is not persuasive, as it confuses DNA copy number with gene expression. By Dr. Smith's characterization, it is quantity of DNA that was measured. Gene *expression*, however, is a process in which DNA is transcribed to produce mRNA, which is then translated to produce protein. The microarray analysis as described by Dr. Smith measures only DNA amounts, and does not measure gene expression. In paragraph 6 this error is perpetuated, as the discussion moves to a correlation of mRNA levels to protein. Once again, this is not pertinent here, as mRNA has not been measured. Accordingly, the results presented in the declaration are concordant with the results presented at page 117 of the specification, but do not bring any additional considerations to bear. Further, the data cannot be independently assessed by the Examiner, as the identification of the tumor samples is sufficiently ambiguous and confusing that the Examiner cannot determine what has been done; the text of the declaration indicates that lung tumor samples were measured, and compared to pooled samples of normal epithelial tissue, and reported as a raw ratio. The average of the normal lung samples was then used to normalize the data to generate a ratio of "expression" of the PRO1800 gene in lung tumor samples compared to the average expression in normal lung tissue. The columns on the data pages are accordingly labeled "Raw Ratio" and "Normalized Ratio". However, a number of the samples include indications of "vs" something, such as "vs25ngEpi1409" or "vs epi pool" or "v normal". These indications are not explained, and appear to indicate some other process of normalization of the data. Accordingly, those lines of data cannot be evaluated by the Examiner. Finally, Dr. Smith indicates that "DNA id" identifies the particular lot of PCR product used; this is not clear; such might reference the batch of enzyme used, or more likely, the DNA sample that was amplified from the primary source. If the latter is the case, then ninety samples were not tested, rather there appear to be only three "lots" of PCR product , i.e. three independent samples represented. Thus, even if there were not confusion between "DNA" and "expression", the Examiner would be unable to perform a meaningful analysis of the evidence presented. Accordingly, the expert's opinion that PRO1800 protein is overexpressed in lung tumors is not accompanied by factual support. Regarding the strength of opposing evidence, the pertinent art has been discussed in the previous Office Action, and above. Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Smith is employed by the assignee.

Finally, applicants have presented arguments to the effect that Example 12 of the Utility Guidelines is not applicable to this case. This is a spurious argument; the Examiner has made no such assertion. However, it is noted that the rejection for lack of utility is maintained in part because contrary to the 'exception' cited by applicants, it has *not* been established that the claimed *protein* is present on any type of tumor cell, in a meaningful amount. This is in direct contrast to the Utility guidelines, which specify that "receptor A *is shown to be present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells.*"

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner